DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-3, 5-24, 26-38, 46-48, and 51 in the reply filed on 12 March 2008 is acknowledged. Claims 39-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Response to Amendment

2. The amendment filed on 20 September 2007 and election filed on 12 March 2008 do not place the application in condition for allowance.

Status of Rejections Pending Since the Office Action of 20 March 2007

3. All rejections of claim 50 are obviated due to cancellation of the claim.

4. All rejections of claims 39-45 are withdrawn due to the withdrawal of these claims following Applicant's election filed on 12 March 2008.

5. All other rejections are maintained.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-3, 5-24, 26-38, 46-48, and 51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is based on the recitations in independent claims 1, 12, 30, 46, 47, and 48 that the separation medium "forms a virtual wall at the fluid interface port that is substantially co-planar with the side wall of the channel" (From claim 1, analogous recitations are present in the other independent claims), and requiring that "no separation medium enters the fluid interface port", along with the argued definition of "co-planar" provided in the first paragraph of page 12 of Applicant's remarks filed on 20 September 2007. If Applicant's definition of "co-planar" is accepted, then there is no way that the limitation that "no separation medium enters the fluid interface port" can be met, rendering the claims indefinite. Applicant argues for a definition of co-planar that requires that the meniscus "must be located along the length of the channel side wall", in which the meniscus is "within the opening" and "replace[s] the removed portion". If this is the case, then some portion of the separation medium must have entered the port, otherwise, the meniscus would be located on the interior side of the channel side wall.

The Examiner's position is that the meniscus cannot rigidly be bound to be <u>entirely</u> within a single plane, since by its nature it is a curved surface. The definition from Webster's Third International Dictionary, that “coplanar” is defined as “lying or acting in the same plane”. Based on these considerations, the most reasonable position seems to the Examiner to be that any meniscus having a portion lying in any

plane defined by the side wall as “coplanar” with the side wall. Unlike Applicant’s proposed reading, this would be consistent with Applicant’s disclosure. (e.g. Figures 4A-4G show menisci that do not correspond to Applicant’s reading; page 10, lines 17-20 describe menisci that do not correspond to Applicant’s reading) In fact, there is no disclosure of a meniscus corresponding to the reading presented in Applicant’s remarks in the specification as originally filed. Therefore the reading relied upon by the Examiner is considered to be appropriate, and is relied upon in the following rejections.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-3, 5-24, 26-38, 46-48, and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (US Patent No. 6,627,406)

In this rejection, undue weight cannot be given to the recitation of “separation” channels or "separation" medium. Specifying an intended use, such as separation, does not structurally define the channels or medium. Therefore, channels having ports as claimed are considered to read on the claims, since they are structurally capable of performing separation, and aqueous medium is considered to read on the instant "separation medium", since it is capable of supporting a separation procedure.

Singh et al teach a separation device comprising one or more reservoirs (Figures 6A-6C; reservoirs 602, 604, or 606) and a plurality of channels connected to the reservoirs (608, 610) having an interior bounded by a side wall (Plate 614); fluid interface ports (612) formed in the side wall of a channel, each port having a depth equal to a thickness of the side wall, and a diameter significantly larger than the depth (Example using system of Figure 6; Column 34, line 65 - Column 35, line 17); wherein an aqueous medium disposed in the channel forms a virtual wall at the fluid interface port having a meniscus that is substantially co-planar with the side wall of the channel

and no medium enters the fluid interface port. (Column 29, lines 6-14; port walls are not wettable, aqueous medium does not rise up the walls) Singh et al teach several channel systems with reservoirs multiplexed to numerous channels. (e.g. Figures 3 and 9-11) Regarding claims 14, 15, and 21, the devices of Singh et al are disclosed as being made from a glass or plastic plate having channels formed therein and a cover plate of the same or different material. (Column 12, lines 36-43)

Singh et al do not explicitly disclose the reservoirs of Figure 6 being anode or cathode reservoirs, nor do they explicitly teach channels multiplexed to reservoirs in the system of Figure 6. Regarding claim 12, Singh et al do not explicitly disclose the arrays of reservoirs in the system of Figure 6.

Singh et al teach the optional provision of electrodes to the reservoirs of their systems for providing electrokinetic fluid motion. (Column 21, lines 8-25 and Column 22, lines 32-50) Singh et al also teach multiplexing the channels of their systems (e.g. Figures 3 and 9-11; Column 6, lines 17-38) to provide flexibility in operation, such as delivery of agents to zones for reaction. Regarding claim 12, Singh et al also teach providing a plurality of channel systems in an array on a substrate. (Figures 11-14) Regarding claim 39, Singh et al disclose forming droplets and directing these droplets of liquid to a zone to make immediate contact with fluid in the channels. (Column 7, line 66 - Column 8, line 5)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Figure 6 of Singh et al by providing electrodes to the reservoirs, as suggested by Singh et al, because it would provide the

ability to manipulate the fluids in the device electrokinetically, as suggested by Singh et al (Column 21, lines 8-25 and Column 22, lines 32-50)

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Figure 6 of Singh et al by multiplexing the channels to numerous other channels and reservoirs, as suggested by Singh et al, because Singh et al teach that this provides desirable flexibility in operation, such as in delivery of different materials to zones for reaction. (Figures 3 and 9-11; Column 6, lines 17-38)

Such provision of electrodes and multiplexing of the channel systems meets the limitations to independent claims 1, 30, 32, 40, 43, and 46-48.

Specific to claim 12, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Figure 6 of Singh et al by providing an array of devices on a single substrate, as shown by Singh et al in Figures 11-14, because such a device geometry would allow facile parallel analyses, the advantageousness of which would have been apparent to anyone having ordinary skill in the art of biochemical analysis.

Specific to claim 39, in the obvious multiplexed system, it would have been obvious to add the required solutions (Column 29, lines 9-11) as droplets directed to the liquid in the channel, as suggested by Singh et al (Column 7, line 66 - Column 8, line 5), because Singh et al suggest this means of adding solutions to the systems of their invention.

Regarding claims 2, 16, 22, 24, and 34, Singh et al suggest such an array. (Column 22, lines 33-40)

Regarding claim 3, the multiplexed systems connect outer regions to inner regions. (Figures 3 and 9-11)

Regarding claim 5, with no fluid travel into ports 612, the dead volume will be zero. (Column 29, lines 7-9)

Regarding claims 6 and 23, Figures 6a and 6c show such an array of ports.

Regarding claims 7, 13, 31, and 33, such choice of size with no change in device operation does not result in patentable distinction over the prior art. In *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 830, 225 USPQ 232 (1984), the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device.

Regarding claims 8-11 and 26-29, Singh et al disclose the systems performing such a variety of analyses. (Column 22, lines 51-55; Column 21, lines 13-25) Regardless, the recitation of an intended use of the device does not further structurally define the device, and the claims are rendered obvious for the reasons given for claims 1 and 12.

Regarding claims 17 and 19, Singh et al also suggest an electrode array integral to the two substrates. (Column 22, lines 33-40; “painting” electrodes) Such an array

would have a particular alignment relative to the reservoirs and ports as claimed in claim 19.

Regarding claims 18 and 35-37, Figures 6a and 6c show regular spacing of the ports. The limitation to a loading device, such as a pipetter or pin, corresponds to intended use, and cannot be given significant weight. The arrangement shown in the figures is considered to be “configured” or “adapted” appropriately for such use.

Regarding claim 20, Figure 6 shows only holes that are reservoirs, which could obviously have electrodes (i.e. anodes or cathodes) as discussed above, or ports. Singh et al disclose adding samples to each port. (Column 29, lines 9-11) Therefore, the number of holes is as claimed.

Regarding claim 38, choice of a radial or other conventional channel pattern is a matter of design choice to a skilled artisan based on which design is most suitable for the peripheral devices to be used with the system. In the absence of evidence that the shape is significant to system operation, such selection of shape does not confer patentability. For instance, in *In re Dailey*, 357 F.2d 669, 149 USPQ 47 (CCPA 1966), the court held that the configuration of the claimed object was a matter of choice which a person of ordinary skill in the art would have found obvious absent persuasive evidence that the particular configuration of the claimed container was significant.

Regarding claim 51, Singh et al teach a droplet generating system including a pin corresponding to the fluid interface port as claimed. (Column 9, lines 11-19)

12. Claims 1-3, 5-11, and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al (WO 99/64850) in view of either McCormick et al or Amigo. Since WO 99/64850 is in German, citations below are given to US Patent No. 6,846,398, which issued from the National Stage entry of this International Application.

Relevant to claims 1 and 46-48, Heller et al disclose a separation device (Figures 1 and 2) comprising: anode and cathode reservoirs (P1 and P2); a plurality of channels connected to the anode reservoirs with each of the channels having an interior bounded by a side wall; a plurality of interface ports (A) formed in the sidewalls of the channels to provide access to the channel, each of the ports having a depth equal to the sidewall (i.e. cover) thickness (Column 6, lines 1-2); with the anode and cathode reservoirs multiplexed with the channels. (Figure 1)

Relevant to claim 2, Heller et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Figure 1; Electrodes E1-E4)

Relevant to claim 3, the device of Heller et al has an outer perimeter (Figure 1), and the central channels S connect a portion of this perimeter to the center of the device.

Relevant to claim 6, Heller et al disclose such an array of apertures (Figures 1 and 2)

Relevant to claim 7, Heller et al disclose channel widths of 20 - several hundred microns, and the port diameter is bounded by the channel width. (Figure 2; Column 4, lines 61-62; Column 5, lines 21-25)

Relevant to claim 8, Heller et al disclose their device being a capillary array electrophoresis plate. (Figure 1; Column 1, lines 5-10)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as “coplanar” with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Heller et al do not explicitly disclose the thickness of their cover, which is pertinent to the dimensional limitations of the instant claims, an interface port wider than it is deep, or a “virtual wall” meniscus.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and methods of Heller et al by specifically using a cover as thin as 10 microns, as taught by either McCormick et al or Amigo,

because the silence of Heller et al concerning this indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs.

Designation of a channel as a “separation” channel in structural limitations is not given undue weight in these rejections, as it points to an intended use of a device rather than defining a specific structure. The presence of the ports of Heller et al in channel sidewalls meets the structural limitations of the claims.

Regarding the independent claims, within this combination, with a channel and port width of twenty to hundreds of microns (Heller et al; Column 4, lines 61-62; Figure 2) and cover thickness of 10 microns, the limitation to a port diameter significantly larger than its depth is met.

Regarding the limitations to a “virtual wall” and requiting that "no separation medium enters the fluid interface port", Heller et al provide no explicit disclosure except that all channels in their system are filled with a separation medium (Column 5, lines 66-67), and therefore a medium/air interface will exist at these ports. Whether the medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. While no explicit channel depth is recited by Heller, a shallow channel could obviously be used (e.g. about twice as wide as it is deep, as conventionally results from isotropic glass etching). An approximately

hemicylindrical 100 micron wide, 50 micron deep channel would have a cross section of 1250π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 100 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant extent, and the meniscus would form at the bottom surface of the wall, leading to no medium entering the port, and a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus would correspond to the instantly claimed “virtual wall”, as no distinction between the respective ports, associated channels, or fluids can be seen.

Specific to claims 9-11, such limitations to intended use of a system do not further structurally define the claimed device, and the claims are therefore rendered obvious for the same reasons cited above regarding claim 1.

13. Claims 12-24 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al in view of Bjornson et al (US 6,284,113) and either McCormick et al or Amigo.

Relevant to claim 12, Heller et al disclose a separation device (Figures 1 and 2) comprising: an array of microfabricated channels (I and S) formed in a substrate and covered by a cover (Column 5, lines 10-12; Column 6, lines 1-2) anode and cathode reservoirs (P1, P2, reservoirs for E3, E4); the channels having an interior bounded by a side wall (i.e. the cover); a plurality of interface ports (A) formed in the sidewalls of the channels to provide access to the channel, each of the ports having a depth equal to the

sidewall (i.e. cover) thickness (Column 6, lines 1-2); with the anode and cathode reservoirs connected at the ends of the channels. (Figure 1)

Relevant to claim 13, Heller et al disclose channel widths of 20 - several hundred microns, and the port diameter is bounded by the channel width. (Figure 2; Column 4, lines 61-62; Column 5, lines 21-25)

Relevant to claims 16 and 22, Heller et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Figure 1; Electrodes E1-E4)

Relevant to claim 18, Heller et al disclose such a regularly-spaced array of apertures (Figures 1 and 2; regular spacing of ports would be provided for the regularly spaced channels)

Relevant to claim 20, the combined number of ports and application areas/holes in Heller et al is as claimed.

Relevant to claim 23, Heller et al show a plurality of ports in channel I. (Figures 1 and 2)

Relevant to claim 26, Heller et al disclose their device being a capillary array electrophoresis plate. (Figure 1; Column 1, lines 5-10)

Regarding claim 12, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as “coplanar” with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Heller et al do not explicitly disclose the thickness of their cover, which is pertinent to the dimensional limitations of the instant claims, an interface port wider than it is deep, a “virtual wall” meniscus, or arrays of anode and cathode reservoirs as claimed.

McCormick et al disclose a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 13, lines 17-22)

Amigo discloses a microfluidic system similar in construction to that of Heller et al, in which they cover the channels with a cover as thin as 10 microns. (Column 8, lines 1-6)

Bjornson et al teach the benefits of highly parallel analyses made possible by providing a large number of microfluidic electrophoresis systems in a single chip. (Figures 6-8; Column 25, line 37 - Column 26, line 54)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device and methods of Heller et al by specifically using a cover as thin as 10 microns, as taught by either McCormick et al or Amigo, because the silence of Heller et al concerning this indicates that a skilled artisan could choose any suitable cover thickness such as those known in the prior art, e.g. McCormick et al or Amigo. The choice of thinner material could be motivated by reduction of material consumption, which could potentially reduce manufacturing costs.

It would also have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Heller et al by providing a chip having an array of the microfluidic devices of Heller et al, as taught by Bjornson et al, because Bjornson et al teach the desirability of parallel analyses being performed in an array of microfluidic devices on a single substrate. The desirability of such parallel capability would have been obvious to a skilled artisan.

Designation of a channel as a “separation” channel in structural limitations is not given undue weight in these rejections, as it points to an intended use of a device rather than defining a specific structure. The presence of the ports of Heller et al in channel sidewalls meets the structural limitations of the claims.

Regarding claim 12, within this combination, with a channel and port width of twenty to hundreds of microns (Heller et al; Column 4, lines 61-62; Figure 2) and cover thickness of 10 microns, the limitation to a port diameter significantly larger than its depth is met.

Regarding the limitations to a “virtual wall” and requiting that "no separation medium enters the fluid interface port", Heller et al provide no explicit disclosure except that all channels in their system are filled with a separation medium (Column 5, lines 66-67), and therefore a medium/air interface will exist at these ports. Whether the medium forms a meniscus at the interior or exterior surface of the port depends on the cross-sectional area of the port vs. that of the channel - fluid will naturally be drawn into the narrower opening, driven by its surface tension. While no explicit channel depth is recited by Heller, a shallow channel could obviously be used (e.g. about twice as wide

as it is deep, as conventionally results from isotropic glass etching). An approximately hemicylindrical 100 micron wide, 50 micron deep channel would have a cross section of 1250π square microns, while the port configuration of Figure 2 of Heller et al for this channel would be a circle with 100 micron diameter, having a cross section twice as large. In the absence of applied pressure, fluid in the channel would not be drawn into the port to a significant extent, and the meniscus would form at the bottom surface of the wall, leading to no medium entering the port, and a port dead volume of substantially zero. Given a conventional flowable separation medium, this meniscus would correspond to the instantly claimed “virtual wall”, as no distinction between the respective ports, associated channels, or fluids can be seen.

Specific to claims 27-29, such limitations to intended use of a system do not further structurally define the claimed device, and the claims are therefore rendered obvious for the same reasons cited above regarding claim 12.

Specific to dependent claims 14, 15, and 21:

In addition to the obviousness arguments made above, Heller et al do not teach the particular materials claimed. Heller et al are silent concerning the materials from which their devices are formed.

Bjornson et al teach making microfluidic devices from glass, plastic, or a combination thereof. (Column 21, lines 35-43)

It would have been obvious to one having ordinary skill in the art to modify the system of Heller et al by forming the device from glass, plastic, or a mixture thereof, as

taught by Bjornson et al, because Bjornson et al teach that such materials are suitable for making microfluidic devices for electrophoresis. The silence of Heller et al on this subject would have caused a skilled artisan to turn to the related prior art, such as Bjornson et al, for teaching of proper materials.

Specific to dependent claims 17, 19, and 24:

In addition to the obviousness arguments made above, Heller et al do not teach electrodes integral to the substrates.

Bjornson et al teach depositing electrodes directly on a microfluidic device, in contact with the reservoirs thereof. (Column 20, lines 39-45)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the system of Heller et al by providing electrodes deposited directly on the substrate in contact with the reservoirs, as taught by Bjornson et al, because this would eliminate the need for manufacture of a separate electrode plate, and simplify electrical connection to the fluids within the device by eliminating concerns regarding precise alignment. Such deposited arrays meet the limitations of these claims.

14. Claims 1-3, 5-8, 12-24, 26, 30-36, 38, and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al in view of Howitz et al.

Relevant to claim 1, Simpson et al disclose a separation device (Column 1, line 65 - Column 2, line 1) comprising: one or more anode reservoirs (Figure 1, 180;

Column 9, lines 25-27)); a plurality of separation channels connected to the anode reservoirs (Column 3, lines 14-28; Column 9, lines 25-27), with each of the separation channels having an interior bounded by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to channel 222); and at least one cathode reservoir multiplexed with two or more separation channels. (Figure 1, Reservoir 120)

Relevant to claim 12, Simpson et al disclose a separation device comprising: an array of microfabricated separation channels formed at the surface of a first microfabricated substrate and a corresponding surface of a second substrate bonded to the surface of the first substrate with each channel having an interior bounded by a sidewall, a first end and a second end (Figures 1 and 4B; Column 9, lines 12-17; Column 4, line 47 - Column 5, line 7); an array of fluid inlets to the separation channels (Figures 1 and 2, B and C with associated channels to channel 222); an array of cathode reservoirs connected to the first end of each of the separation channels (Figure 1; Column 9, lines 23-24); and an array of anode reservoirs, wherein at least one anode reservoir is connected to the respective second ends of at least two of the separation channels. (Figure 1; Column 9, lines 25-27)

Relevant to claims 30 and 32, Simpson et al disclose a separation device comprising: a substrate (Column 4, line 47 - Column 5, line 7); a plurality of separation channels formed in the substrate (Column 3, lines 14-28), each channel having an interior bound by a side wall (Figure 4B; Column 4, line 47 - Column 5, line 7); a plurality of fluid inlets to the separation channels (Figure 2, B and C with associated channels to

channel 222); an anode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 180; Column 10, lines 49-57); and a cathode reservoir multiplexed to two or more separation channels (Figure 1, Reservoir 120; Column 10, lines 58-65)

Relevant to claims 2, 16, 17, 22, and 34, Simpson et al disclose an electrode array coupled or coupleable to the reservoirs and fluid inlets within the separation device. (Column 5, line 36 - Column 6, line 37; Column 10, lines 9-10) This array can be in electrical contact with the device (Figure 4B; Column 10, lines 31-33), or integral with the substrates of the device (Column 10, lines 11-13).

Relevant to claim 3, Simpson et al disclose a separation device with an outer perimeter and a center, with the separation channels connecting the outer perimeter to the center. (Figure 9; Column 9, lines 9-11)

Relevant to claims 8 and 26, Simpson et al disclose their device being a capillary array electrophoresis plate. (Column 1, lines 65-66)

Relevant to claim 14, Simpson et al disclose the first and second substrates being made of glass. (Column 9, lines 66-67)

Relevant to claim 15, Simpson et al disclose the first and second substrates being made of plastic. (Column 10, lines 1-2)

Relevant to claims 18 and 35, Simpson et al disclose the regular spacing of the fluid inlets on one of the substrates to receive solutions from a parallel loading device. (Column 1, lines 13-15; Column 4, line 47 - Column 5, line 7)

Relevant to claims 19 and 24, Simpson et al disclose the first substrate of their device including an array of electrodes aligned with sample reservoirs of the device to

make electrical contact with solutions in the sample, waste, anode, and cathode reservoirs. (Column 10, lines 17-23)

Relevant to claim 20, Simpson et al disclose a number of holes, H, approximately equal to 5N/4, where N is the number of samples to be processed. (Column 10, lines 24-27)

Relevant to claim 21, Simpson et al disclose their device being made of a combination of glass and plastic. (Column 10, lines 28-30)

Relevant to claim 23, Simpson et al disclose a plurality of sample fluid inlets in communication with on of the separation channels (e.g. Figure 2, B and C both feed channel 222)

Relevant to claim 36, Simpson et al disclose a parallel loading device comprising a multi-headed pipetter. (Column 11, lines 16-18)

Relevant to claim 38, Simpson et al disclose the disposition of the separation channels in a radial pattern on the separation device. (Figure 9)

Regarding the independent claims, a meniscus that forms anywhere from the upper to lower surface of the interface port can be described as “coplanar” with the sidewall channel. Such menisci will inherently exist in this device filled with a flowable separation medium.

Simpson et al do not explicitly disclose a device comprising: fluid interface ports formed in the side walls of the separation channels to provide access to the interiors of the separation channels, wherein the diameter of the port is significantly larger than its

depth, wherein a separation medium disposed in the interior of the separation channel forms a virtual wall at each fluid interface port, and wherein no separation medium enters the fluid interface port (Claim 1), zero dead volume (Claim 5), or diameters between 25 and 125 µm. (Claims 7, 13, 25, 31, 33) They also do not explicitly disclose a fluid interface port that comprises an array of apertures forming virtual walls. (Claim 6)

Regarding claim 39, Simpson et al do not explicitly disclose forming a droplet from the liquid sample, or directing the droplet to a virtual wall formed by a separation medium in a fluid interface port formed in the sidewall of a separation channel.

Regarding claims 40-45, they also do not explicitly disclose a method comprising forming the plurality of ports in the channel sidewalls by removing portions of the sidewalls to define ports with diameters between 25 and 125 µm.

Howitz et al disclose a device (Figure) comprising: fluid interface ports (capillaries containing menisci 6) formed in the side wall of a fluid channel (9) to provide access to the interior of the fluid channel, wherein a separation medium disposed in the interior of the fluid channel forms a virtual wall at each fluid interface port (Menisci 6). (Column 3, lines 11-15) Relevant to claim 6, they also disclose a fluid interface port comprising an array of apertures forming virtual walls.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the device of Simpson et al by replacing the sample and waste reservoirs, and their associated side channels with a simple hole or holes through

the sidewall to serve as a fluid port, as taught by Howitz et al, because Howitz et al teach the usefulness of their fluid port in introducing fluids to microchannels while preventing outflow of the fluid contained within the channel. (Column 1, lines 53-58) It would also reduce the number of holes required in the device by eliminating the need for injection crosses, this reduction in the number of holes having been taught by Simpson et al to be desirable. (Column 3, lines 50-65)

Further addressing claims 1 and 5, given the definition of dead volume presented in the instant specification (roughly, the volume of liquid held in the port and not flowing with the fluid within the channel), the dead volume associated with ports such as those of Howitz et al will be variable, as a function of the affinities of the fluids for the surface of the port, among other factors. (Column 3, lines 25-31) As such, the dead volume will be zero or near zero (i.e. less than 1 picoliter) for a clean hydrophobic port surface in a device using aqueous fluids. Such hydrophobicity is an innate property of many polymers known to be useful in manufacturing microfluidic devices (e.g. fluoropolymers) or it could be achieved by using known surface treatments for glass (hexamethyldisilazane, used by Simpson - Column 4, lines 53-56) and silicon (Hydrofluoric acid), and would constitute an obvious modification of the device, because such a surface would minimize loss of the injected sample. (i.e. if an aqueous sample hit a hydrophobic surface in a port configured in the way shown in the Figure of Howitz et al, substantially the entire droplet would immediately fall into contact with the fluid in channel 9, as the contact angle and reduced frictional force would not be sufficient to retain the droplet on this surface)

Regarding the limitation that the port be wider than it is deep, although the example given by Howitz et al does not meet this limitation, Howitz et al also disclose variation of the depth of the port. (i.e. length of the capillary; Column 2, lines 5-10 and 27-30) Choice of a shorter length such that this limitation is met would have been obvious to a skilled artisan, particularly given the trend towards miniaturization in this art.

Further addressing claim 20, by replacing each sample reservoir with a fluid interface port, and eliminating waste reservoirs, the number of holes in this combination device would be reduced to N+A+C, where N is the number of samples to be analyzed, A is the number of anode reservoirs, and C is the number of cathode reservoirs.

Regarding claims 46-48, each of these claims fully encompasses claim 1 in that they only recite limitations that are present in claim 1, while removing various other limitations. The prior art as applied to claim 1 above therefore also renders these claims obvious, given their open language (i.e. “comprising”).

15. Claims 9-11 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claims 1 and 12 above, and further in view of Bjornson et al. (US 6,103,199)

Simpson et al and Howitz et al disclose combinations as described above in addressing claims 1 and 12.

Neither Simpson et al nor Howitz et al disclose their devices being used for electrochromatography (Claims 9 and 27), pressure-driven chromatography (Claims 10 and 28), or isoelectric focusing (Claims 11 and 29).

Bjornson et al disclose electrophoretic devices used for isoelectric focusing and capillary chromatography. (Column 12, lines 53-59) They also disclose fluid flow in their devices by electroosmosis (Column 11, lines 55-60), which suggests electrochromatography. (i.e. chromatography in which the motion of the mobile phase is caused by an electric field)

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of Simpson et al and Howitz et al by providing the separation capillaries with a chromatographic medium, immobilized pH gradient, or ampholytes and using the device for electrochromatography or isoelectric focusing, as taught by Bjornson et al, because it would provide useful analytical data about the analytes. It would be well within the abilities of one having ordinary skill in the art to use the channel structure shown by Simpson et al with any known prior art capillary electrophoretic technique, such as those claimed here.

Additionally, electroosmotic force corresponds to a type of pressure driving a fluid through a capillary, and as such, is considered a form of pressure-driven chromatography.

16. Claims 37 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Simpson et al and Howitz et al as applied to claim 36 above, and further in view of Sundberg et al.

Simpson et al and Howitz et al disclose a combination as described above in addressing claim 36. Simpson et al and Arnold et al also disclose a combination as described above in addressing claim 36.

None among Simpson et al, Howitz et al, and Arnold et al disclose a parallel loading device comprising a pin corresponding to a fluid interface port and for carrying and introducing the droplet of a liquid sample to the fluid interface port by contacting the virtual wall.

Sundberg et al disclose a parallel loading device (Figure 2) comprising a pin (38) for carrying and introducing the droplet of a liquid sample (36) to the ports (34) of a microfluidic system.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the combination of either Simpson et al and Howitz et al or Simpson et al and Arnold et al by providing a parallel loading device comprising pins for carrying liquid samples to the fluid interface port, as taught by Sundberg et al, because it would simplify delivery of small droplets. It would be well within the abilities of one having ordinary skill in the art to choose any known means of delivering fluid droplets to a selected spot in a microfluidic device (i.e. the port), such as that taught by Sundberg et al. A technique that delivers a plurality of droplets simultaneously, such as

that of Sundberg et al, would be particularly obvious to choose, because it would aid in increasing throughput, decreasing labor, etc.

Response to Arguments

17. Applicant's arguments filed 20 September 2007 have been fully considered but they are not persuasive.

Regarding the definition of coplanar, Applicant argues that the plane of the meniscus is equal to, not a subset of the coplanar plane of the side wall. This is problematic for at least the following reasons: (a) a meniscus is not planar, (b) numerous planes are defined by the side wall, including the plane of its upper and lower surfaces, (c) no such narrow definition of “coplanar” is supported by the original disclosure. The meniscus cannot rigidly be bound to be <u>entirely</u> within a single plane, since by its nature it is a curved surface. The definition from Webster’s Third International Dictionary, that “coplanar” is defined as “lying or acting in the same plane”. Based on these considerations, the Examiner believes the most reasonable interpretation of this term to be that any meniscus having a portion lying in any plane defined by the side wall is “coplanar” with the side wall. Unlike Applicant’s proposed reading, this would be consistent with Applicant’s disclosure. (e.g. Figures 4A-4G show menisci that do not correspond to Applicant’s reading; page 10, lines 17-20 describe menisci that do not correspond to Applicant’s reading) In fact, there is no disclosure of a meniscus corresponding to the reading presented in Applicant’s remarks in the specification as originally filed. Therefore the reading relied upon by the Examiner is

considered to be the appropriate one. In addition, Applicant's proposed definition raises issues under 35 U.S.C. §112, second paragraph (Note rejection under this statute above), as Applicant interprets "co-planar" to require positioning of the meniscus within the port, while the limitation that "no separation medium enters the fluid interface port" precludes the meniscus from lying within the port.

Applicant argues that Singh requires the solution in the device to substantially fill well 612. This is incorrect. Note Column 29, lines 6-14 as cited in the rejection.

Applicant further argues that Singh et al fails to disclose a fluid interface port having a diameter significantly larger than the depth. This is also incorrect. Note Column 34, line 65 - Column 35, line 17 as cited in the rejection, which teaches a port 1 mm in diameter and 900-950 micrometers in height. In addition, the Examiner notes that in *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 830, 225 USPQ 232 (1984), the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device. No such difference in operation is evident in the instant case.

Applicant further argues that the rejections variously relying on Heller, McCormick, Amigo, Simpson, Howitz, Bjornson and/or Sundberg do not render the claims obvious, as they do not teach devices in which none of the separation medium

enters a fluid interface port. The Examiner disagrees and believes the claimed structure is obvious for the reasons cited in the rejections above.

Applicant argues that Heller's teaching of an enlarged application area A somehow teaches away from the claimed structure. No evidence is given that the size of the application areas have any relation to the structure recited in the claims. The purported advantages cited are features that are not described in the claims.

Applicant argues that the references do not disclose a fluid interface port forming a virtual wall that replaces a removed portion of a side wall or a meniscus that is co-planar with a side wall of a channel. The references teach media filling channels having ports that are structurally the same as those instantly disclosed and claimed. In the absence of any evidence to the contrary, the Examiner maintains that fluids will behave in these systems in the same way they behave in Applicant's system. Any recited limitations that merely describe the way in which a fluid behaves in a channel having a hole in its side must be considered inherent over the structures taught, for example, by Heller et al or Singh et al, because the channel/port structures taught by these references are the same as those instantly claimed. Once liquid is added to the channels, the liquid must be considered to behave precisely the same as long as there is no structural difference between the claims and the prior art. Applicant must claim structure that distinguishes the claimed subject matter from the prior art in order for the claims to be allowable.

Regarding Applicant's arguments concerning Howitz et al, Applicant is once again directed to the discussion of the reference within the rejection. In any event,

Applicant's proposed definition of "co-planar" also requires the fluid to spread into the fluid interface port, in order to provide a meniscus located along the length of the channel side wall, so it is unclear whether fluid entering the ports is intended to be excluded by the claim language.

Applicant argues that if the prior art were modified as suggested by the Examiner, it would be inoperable for its intended purpose, because the efficiency of loading would be compromised by the smaller fluid interface port. There is nothing in the Howitz reference that indicates that any reduction in efficiency would result from miniaturization, and nowhere in the rejections is the size of the port openings in Howitz altered - the Examiner relies on Howitz's teaching that capillary length can be altered, but this requires no modification of port opening size.

Applicant also argues that substantial reconstruction and redesign would be required in the combinations made, as well as a change in the basic principle of operation. It is not clear which rejection Applicant is referring to, but no particular redesign of Heller et al is made in the rejections above - the most substantial secondary teaching is cover thickness. In Simpson et al, one injection means is replaced by that of Howitz, which is advantageous for the reasons given in Howitz. This hardly constitutes substantial redesign, and there is no change in basic principles of operation contemplated in the rejections above.

Applicant further argues that there is no reasonable expectation of success from the combinations. All secondary references teach structures that are used for the same purpose in the combination as in the original references, all are taken from analogous

art, and proper motivations from the references are presented, therefore there is a reasonable expectation of success. A prima facie case of obviousness is thus made, and applicant's unsupported assertion that there is no expectation of success is not sufficient to overcome the rejections.

Conclusion

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Jeffrey T. Barton whose telephone number is (571)272-1307. The examiner can normally be reached on M-F 9:00AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nam Nguyen can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JTB
19 June 2008

/Edna Wong/
Primary Examiner, Art Unit 1795